Chlorthalidone vs. Hydrochlorothiazide in Hypertension

DISCLOSURE INFORMATION:
Dr. Elliott has received research funding, honoraria, and/or travel expenses from essentially every pharmaceutical company that makes, markets, or distributes antihypertensive drugs in the United States. A former full-time employee of RUSH Medical College, he was prohibited from (and still does not) own individual stocks or financial instruments related to healthcare.
DISCLOSURE OF RELATIONSHIPS

For William J. Elliott over the past 12 months,

Grant/Research Support: None.

Consultant: None.

Speakers Bureau: None.

Stock shareholder: None! I once worked at RUSH!!!

Other Support, Tangible or Intangible: Elsevier (Division of Harcourt), UpToDate®, Springer
Affidavit of Originality

• The following material is based exclusively on the speaker’s own opinion, knowledge and expertise.

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• The information presented is based on the principles of “Evidence-Based Medicine,” and is intended to avoid promotion of any specific commercial interest, product, or company.
“Off-Label Use” Disclaimer

WARNING!
During this discussion, attempts will be made to avoid discussion of “off-label” or investigational use of drugs, but very few antihypertensive drugs have been approved by the US FDA to prevent cardiovascular events or end-stage renal disease, which most agree is the major reason to diagnose and treat hypertension. In addition, some of the doses of the diuretics discussed have not yet been approved for hypertension.

DISCLAIMER:
The audience member should interpret each example and every statement in the context of the “local standard of care” regarding medical practice, and judge each allegation regarding drug therapy within the standards approved by the most current product information for each marketed agent, as reflected in the most recent FDA-approved package insert. The speaker assumes no liability for any erroneous interpretation of the information contained herein, stated or implied.
Chlorthalidone vs. Hydrochlorothiazide in Hypertension

William J. Elliott, M.D., Ph.D.
Pacific Northwest University of Health Sciences, Yakima, WA
Learning Objectives

At the end of this 45-minute presentation, the awake audience member should be able to compare and contrast chlorthalidone (CTD) and hydrochlorothiazide (HCTZ), with respect to:

– Pharmacokinetics and pharmacodynamics.
– Blood pressure-lowering efficacy.
– Safety.
– Efficacy in preventing cardiovascular events (especially heart failure).
Pharmacokinetics and Pharmacodynamics
## Chlorthalidone vs. HCTZ

<table>
<thead>
<tr>
<th>Property</th>
<th>Chlorthalidone</th>
<th>HCTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination $t_{1/2}$</td>
<td>0.4-12 hr (single)</td>
<td>0.6-9 hr (single)</td>
</tr>
<tr>
<td></td>
<td>0.5-48 (multiple)</td>
<td>0.8-15 (multiple)</td>
</tr>
<tr>
<td>Duration of effect</td>
<td>24-72 hours</td>
<td>6-12 hours</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>0.4-6 hr</td>
<td>0.2-4 hr</td>
</tr>
<tr>
<td>$t_{\text{onset}}$ (diuresis)</td>
<td>0.2-0.6 hr</td>
<td>0.2-0.4 hr</td>
</tr>
<tr>
<td>Doses (mg/d)</td>
<td>(15), 25, 50, 100</td>
<td>12.5, 25, 50, 100</td>
</tr>
</tbody>
</table>

*Hypertension. 2004;43:4-9*
Current Combinations Containing HCTZ

- **ACE-Inhibitors** (captopril, enalapril, lisinopril, benazepril, quinapril, fosinopril, moexipril)
- **ARBs** (losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan, olmesartan)
- **Beta-blockers** (propranolol, metoprolol, timolol, bisoprolol)
- **Centrally-Acting Drugs** (guanethidine, methyldopa, reserpine, clonidine)
- **Renin inhibitor** (aliskiren)
- **Other Diuretics** (triamterene, amiloride, spironolactone)
- **Triple Combos** (reserpine + hydralazine; valsartan + amlodipine; olmesartan + amlodipine; aliskiren + amlodipine)
Current Combinations Containing Chlorthalidone

- **Atenolol** (Tenoretic®, AstraZeneca, Wilmington, DE)
  - 25/50, 25/100 mg
- **Clonidine** (Combipres®, Boehringer Ingelheim, Ridgefield, CT)
  - 15/0.1, 15/0.2 mg
- **Reserpine** (Regroton®, Demi-Regroton®, Sanofi-aventis, Bridgewater, NJ)
  - 50/0.25, 25/0.125 mg
- **Azilsartan** (Edarbyclor®, Arbor Pharmaceuticals, Atlanta, GA)
  - 40/12.5, 40/25 mg
Blood Pressure-Lowering Effects
# Chlorthalidone vs. HCTZ

<table>
<thead>
<tr>
<th>Author (year), n</th>
<th>Doses</th>
<th>ΔBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowlus (1964), n=19</td>
<td>HCTZ 100 mg/d&lt;br&gt;Chlor 50 mg/d</td>
<td>18/8&lt;br&gt;25/10</td>
</tr>
<tr>
<td>Finnerty (1976), n=56</td>
<td>HCTZ 50 mg bid&lt;br&gt;Chlor 50 mg/d</td>
<td>22/16&lt;br&gt;18/15</td>
</tr>
<tr>
<td>Clark (1979), n=126</td>
<td>HCTZ 25 mg/d*&lt;br&gt;HCTZ 50 mg/d*&lt;br&gt;Chlor 25 mg/d</td>
<td>15/8†&lt;br&gt;18/12&lt;br&gt;25/16</td>
</tr>
<tr>
<td>van Soeren (1980), n=25</td>
<td>HCTZ 50 mg/d*&lt;br&gt;Chlor 50 mg/d</td>
<td>9/3&lt;br&gt;14/9</td>
</tr>
</tbody>
</table>

*with triamterene; †P < 0.05 vs. chlorthalidone
Summary: Chlorthalidone vs. HCTZ

∆BP from Baseline (mm Hg)

HCTZ 50 mg/d: -16.5
HCTZ 100 mg/d: -20.4
Chlorthalidone 50 mg/d: -21.5

Systolic BP
Diastolic BP

Chlorthalidone vs HCTZ: Dosing Equivalence?

50 mg HCTZ ~ 25 to 37.5 mg chlorthalidone

*Hypertension*. 2004;43:4-9
**Dose-Response Meta-Analysis**

<table>
<thead>
<tr>
<th></th>
<th>HCTZ (n=108)</th>
<th>CTD (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of data points</td>
<td>6063</td>
<td>4380</td>
</tr>
<tr>
<td>Duration (weeks)</td>
<td>10.6±8.5</td>
<td>32.2±21.3</td>
</tr>
<tr>
<td>Dose (mg, mean±S.D.)</td>
<td>42.7±37.1</td>
<td>31.6±25.2</td>
</tr>
<tr>
<td>Median dose (mg)</td>
<td>33.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Dose range (mg)</td>
<td>3-450</td>
<td>12.5-200</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>162.8±8.6</td>
<td>165.8±9.0</td>
</tr>
<tr>
<td>ΔSBP (mm Hg)</td>
<td>-17±5.6</td>
<td>-23±6.7</td>
</tr>
<tr>
<td>Median ΔSBP (mm Hg)</td>
<td>-17</td>
<td>-25</td>
</tr>
<tr>
<td>Serum [K⁺] (mEq/L)</td>
<td>4.22±0.12</td>
<td>4.38±0.14</td>
</tr>
<tr>
<td>Δ[K⁺] (mEq/L)</td>
<td>-0.36±0.19</td>
<td>-0.45±0.16</td>
</tr>
<tr>
<td>Median Δ[K⁺] (mEq/L)</td>
<td>-0.31</td>
<td>-0.40</td>
</tr>
</tbody>
</table>

*Am J Hypertens. 2010;23:440-6*
Dose-Response Meta-Analysis

Am J Hypertens. 2010;23:440-6

Dose (mg/d)

ΔSBP (mm Hg)

HCTZ

CTD
Dose-Response Meta-Analysis

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>∆SBP (mm Hg)</th>
<th>HCTZ (n = 2848)</th>
<th>Chlorthalidone (n = 2995)</th>
<th>HCTZ (n = 1665)</th>
<th>CTD (n = 787)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5-25 mg/d</td>
<td>-14</td>
<td>-14</td>
<td>-16</td>
<td>-18</td>
<td>-20</td>
</tr>
<tr>
<td>25.1-37.5 mg/d</td>
<td>-24</td>
<td>-24</td>
<td>-26</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>37.8-60 mg/d</td>
<td>-26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05

*Am J Hypertens. 2010;23:440-6*
# Dose-Response Meta-Analysis

Systolic BP Changes NOT EQUIVALENT at threshold of 4 mm Hg (by Schuirmann’s Test)

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>SBP Change (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5-25 mg/d</td>
<td>-14</td>
</tr>
<tr>
<td>25.1-37.5 mg/d</td>
<td>-24</td>
</tr>
<tr>
<td>37.8-60 mg/d</td>
<td>-16</td>
</tr>
<tr>
<td>75-80 mg/d</td>
<td>-20</td>
</tr>
<tr>
<td>80-90 mg/d</td>
<td>-20</td>
</tr>
</tbody>
</table>

Am J Hypertens. 2010;23:440-6
Chlorthalidone vs. HCTZ

Chlorthalidone
12.5, then 25 mg/d
x 4 wks each

HCTZ
25, then 50 mg/d
x 4 wks each

Placebo
x 4 wks

ABPM

n=30

Placebo
x 4 wks

ABPM

ABPM

Hypertension. 2006;47:352

Office BP Measurements
Hypertension. 2006;47:352

A significant “Carry-over Effect”
Chlorthalidone vs. HCTZ

30 Hypertensive patients were given 12.5 mg/d of chlorthalidone or 25 mg/d of HCTZ x 4 wks, and the doses doubled for 4 wks.

- SBP on ABPM @ 8 wks: P = 0.056
- SBP (nighttime) @ 8 wks: P = 0.009
- Office SBP @ 2 Wks: P < 0.001

*Hypertension. 2006;47:352*
ABPM: HCTZ vs. Other Drugs

**HCTZ 12.5-25 mg/d**

- **14 Trials**
  - Systolic BP: -12.9
  - Diastolic BP: -13.3

**ACE-I 5 Trials**

- Systolic BP: -6.5
- Diastolic BP: -7.7

**ARB 7 Trials**

- Systolic BP: -8
- Diastolic BP: -8.1

**β-blocker 3 Trials**

- Systolic BP: -11.2
- Diastolic BP: -11

**CCB 5 Trials**

- Systolic BP: -12
- Diastolic BP: -5.4

**HCTZ 50 mg/d**

- 5 Trials

*J Am Coll Cardiol. 2011;57:590-600*
HCTZ Dose-Response: Δ24-hr ABPM

Δ in 24-hour ABPM (mm Hg)

-14
-12
-10
-8
-6
-4
-2
0

ΔSBP
ΔDBP
ΔSystolic BP

12.5 mg/d
-5.7
4 studies;
129 subjects

25 mg/d
-7.8
9 studies;
503 subjects

50 mg/d
-12
****
5 studies;
123 subjects

J Am Coll Cardiol. 2011;57:590-600
“Switch:” HCTZ to Chlorthalidone

$P < 0.03$

Systolic BP (mm Hg)

HCTZ

Chlorthalidone

J Clin Hypertension (Greenwich). 2005;7:354
Azilsartan 40 mg: + CTD or + HCTZ


Change in Office BP (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>DBP</th>
<th>SBP</th>
<th>DBP</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline BP: 165/96</td>
<td></td>
<td>Baseline BP: 164/96</td>
<td></td>
</tr>
<tr>
<td>2 wks</td>
<td>-19.8 **</td>
<td>-7.1 *</td>
<td>-35.1 ***</td>
<td>-15 ***</td>
<td>-37.8 ***</td>
<td>-32.8 ***</td>
</tr>
<tr>
<td>6 wks</td>
<td>-18.8 **</td>
<td>-6</td>
<td>-29.5</td>
<td>-11.2</td>
<td>-16.4 ***</td>
<td>-13.7 ***</td>
</tr>
<tr>
<td>10 wks</td>
<td>n = 295</td>
<td>n = 292</td>
<td>n = 295</td>
<td>n = 292</td>
<td>n = 295</td>
<td>n = 292</td>
</tr>
</tbody>
</table>
Azilsartan 40 mg: + CTD or + HCTZ

Change in ABPM (mm Hg)

**SBP**
- Chlorothalidone 25 mg: -25.7
- HCTZ 25 mg: -19.9

DBP
- Baseline BP: 147/86
  - 6 wks: -14.7
  - 10 wks: -22.4

**SBP**
- Baseline BP: 145/86
  - 6 wks: -28.6
  - 10 wks: -28.6

**DBP**
- Baseline BP: 145/86
  - 6 wks: -15.2
  - 10 wks: -12.6

Safety
Diuretics: Adverse Effects

• **Dose-dependent:**
  – Hypotension (esp. orthostatic), volume depletion, polyuria
  – Hypokalemia, hypomagnesemia, (hyponatremia)

• **Erectile dysfunction**
  – May be more common with thiazides than with other commonly-used antihypertensive drugs

• **Metabolic Adverse Effects:**
  – Hyperglycemia (and increased risk of incident diabetes)
  – Hypercholesterolemia
  – Hyperuricemia
  – The clinical importance of these is very controversial!
Dose-Response Meta-Analysis

Am J Hypertens. 2010;23:440-6

Dose (mg/d)

$\Delta [K^+]$ (mEq/L)

HCTZ

CTD
Dose-Response Meta-Analysis

Changes in serum [K+] ARE EQUIVALENT at threshold of 0.29 mEq/L (by Schuirmann’s Test)

Am J Hypertens. 2010;23:440-6
HCTZ vs. CTD in MRFIT

• In 1973, the Multiple Risk Factor Intervention Trial (MRFIT) randomized 8012 hypertensive men to either “Special Intervention” or “Referred Care.”

• In addition to advice about diet, exercise, and smoking cessation, the “Special Intervention” group received either initial HCTZ or CTD (followed by other agents) at the discretion of the principal investigator at each site.

• This is the only trial that provides (non-randomized) direct, simultaneous comparisons for HCTZ vs. CTD.
  – These comparisons may be confounded by treatment assignment (SI vs. RC), dose, secular trends, and others.
HCTZ vs. CTD in MRFIT

Overall $P = 0.1595$

HCTZ (n=4049)

CTD (n=2392)

Glucose (mg/dL)

Years of Follow-Up

*P < 0.05

Hypertension. 2011;57:689-94.
Network Meta-analysis: New DM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB</td>
<td>0.62 (0.51-0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE-I</td>
<td>0.67 (0.57-0.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.75 (0.63-0.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>CCB</td>
<td>0.79 (0.67-0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>(\beta)-blocker</td>
<td>0.93 (0.78-1.11)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Diuretic Referent

Incoherence = 0.054

Updated from *Lancet.* 2007;369:201
Network Meta-analysis: New DM

ARB 0.85 (0.68-1.00) p=0.055
ACE-I 0.90 (0.78-1.04) p=0.16
Placebo Referent
CCB 1.05 (0.90-1.24) p=0.53
β-blocker 1.25 (1.05-1.48) p=0.01
Diuretic 1.34 (1.12-1.60) p=0.001

Odds Ratio for Incident Diabetes

Updated from Lancet. 2007;369:201

Incoherence = 0.054
Network Meta-analysis: New DM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB</td>
<td>0.83 (0.69-1.01)</td>
<td>0.061</td>
</tr>
<tr>
<td>ACE-I</td>
<td>0.88 (0.75-1.03)</td>
<td>0.119</td>
</tr>
<tr>
<td>Placebo</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>1.04 (0.88-1.24)</td>
<td>0.622</td>
</tr>
<tr>
<td>β-blocker</td>
<td>1.22 (1.01-1.47)</td>
<td>0.035</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>1.25 (1.00-1.59)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Updated from *Lancet*. 2007;369:201

Incoherence = 0.069
Network Meta-analysis: New DM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds Ratio</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB</td>
<td>0.86</td>
<td>(0.70-1.07)</td>
<td>0.175</td>
</tr>
<tr>
<td>ACE-I</td>
<td>0.94</td>
<td>(0.78-1.13)</td>
<td>0.537</td>
</tr>
<tr>
<td>Placebo Referent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>1.10</td>
<td>(0.91-1.34)</td>
<td>0.336</td>
</tr>
<tr>
<td>β-blocker</td>
<td>1.31</td>
<td>(1.07-1.61)</td>
<td>0.010</td>
</tr>
<tr>
<td>No Chlorthalidone</td>
<td>1.48</td>
<td>(1.16-1.90)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Incoherence = 0.095

Updated from *Lancet*. 2007;369:201
Other Biochemical Data: MRFIT

- Compared to MRFIT men receiving HCTZ, those receiving CTD had:
  - **Lower** serum LDL-cholesterol (144±3 v. 148±3 mg/dL at year 6, *P* = 0.009, primarily in year 1)
  - **Lower** serum total cholesterol (232±3 v. 237±3 mg/dL at year 7, *P* < 0.0001, primarily in years 1-2, 4-5)
  - **Lower** serum potassium (4.0±0.05 v. 3.8±0.05 at year 7, *P* = 0.003, seen in all years)
  - **Higher** serum urate (7.24±0.05 v. 7.18±0.05, *P* = 0.001 primarily seen in years 1-3)
Contraindications & Warnings

• Thiazides:
  – Contraindicated in anuria, allergic patients (sulfonamides)
    • Typical manifestations: skin rash, sun sensitivity
  – Less effective if eGFR < 40-45 mL/min (use loop instead)

• Loop:
  – Contraindicated in anuria, hepatic coma, electrolyte disorders (NOS)
  – Furosemide, bumetanide twice-daily for hypertension

• Potassium-sparing:
  – Contraindicated if [K+] > 5.5 mEq/L, CrCl < 30 mL/min
  – May cause dangerous (fatal?) hyperkalemia (with salt substitutes, ACE-I, ARB, high-potassium foods, NSAIDs)
Diuretics: Drug Interactions

• **All Diuretics:**
  – Digitalis, lithium, NSAIDs
  – Alcohol, CNS depressants (risk: orthostatic hypotension)
  – Corticosteroids, ACTH, amphotericin B (hypokalemia)
  – Alter excretion of anionic drugs (e.g., salicylates)
  – Potentiate BP-lowering of other antihypertensive drugs

• **Thiazides:**
  – Potentiate non-depolarizing muscle relaxants, antagonize norepinephrine, interfere with parathyroid tests

• **Loop:**
  – Antagonize tubocurarine, potentiate succinyl choline
  – More ototoxicity with other ototoxic drugs (aminoglycosides)

• **Potassium-sparing:**
  – Eplerenone: CYP3A4 inhibitors (-azole, etc.)
Efficacy in Preventing Cardiovascular Events in Clinical Trials?
Chlorthalidone vs. HCTZ

- MRFIT decreed after 5 years of follow-up: “Only chlorthalidone should be used.”
  - SI Men given HCTZ had 44% more CHD, 16% more death than their RC controls.
  - SI Men given CTD had 58% less CHD, 41% less death than their RC controls.

- After switch to only chlorthalidone:
  - SI Men originally given HCTZ had 28% less CHD, 26% less death than their RC controls ($P = 0.04, 0.06$)

- In the long-term (10+ years), RC men got HCTZ, SI men got CTD (after 1980), and SI men had fewer CVD events!
### Baseline Characteristics: MRFIT

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCTZ</th>
<th>CTD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>46.9±5.9</td>
<td>46.7±5.7</td>
<td>0.1234</td>
</tr>
<tr>
<td>History of HBP</td>
<td>67.7%</td>
<td>65.3%</td>
<td>0.0647</td>
</tr>
<tr>
<td>Smoker</td>
<td>55.4%</td>
<td>56.3%</td>
<td>0.4827</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>27.8±3.5</td>
<td>27.8±3.4</td>
<td>0.7393</td>
</tr>
<tr>
<td>MRFIT SI Group</td>
<td>44.8%</td>
<td>83.9%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Any BP Pill</td>
<td>34.7%</td>
<td>29.1%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diuretic (R_x)</td>
<td>31.2%</td>
<td>26.2%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Dose &gt; 50 mg/d</td>
<td>28.4%</td>
<td>47.9%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Adapted from *Hypertension*. 2011;57:689-94.
MRFIT: Risk of CVD Events

Adapted from Hypertension. 2011;57:689-94.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>aHR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>1.15 (0.52-2.55)</td>
<td>0.6959</td>
</tr>
<tr>
<td>MI by clinical criteria</td>
<td>2.62 (1.85-3.62)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MI by EKG</td>
<td>1.88 (1.27-1.73)</td>
<td>0.0103</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.33 (0.58-3.04)</td>
<td>0.4837</td>
</tr>
<tr>
<td>CABG</td>
<td>2.37 (1.74-3.26)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVH by EKG</td>
<td>0.95 (0.60-1.49)</td>
<td>0.8114</td>
</tr>
<tr>
<td>Angina by Rose ?aire</td>
<td>1.36 (1.10-1.69)</td>
<td>0.0029</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.89 (0.21-3.73)</td>
<td>0.9229</td>
</tr>
<tr>
<td>Occlusive PAD</td>
<td>1.65 (1.04-2.60)</td>
<td>0.0218</td>
</tr>
</tbody>
</table>

Adapted from *Hypertension*. 2011;**57**:689-94.
Indirect Comparisons: CTD v. HCTZ

• ALLHAT vs. ANBP-2:
  – ALLHAT: Chlorthalidone better than ACE-I (lisinopril)
  – ANBP-2: ACE-I (enalapril) better than HCTZ
  – Conclusion: Chlorthalidone is better than HCTZ

• ALLHAT vs. ACCOMPLISH
  – ALLHAT: Chlorthalidone better than CCB (amlodipine)
  – ACCOMPLISH: CCB (+ benazepril) better than HCTZ (+ benazepril)
  – Conclusion: Chlorthalidone is better than HCTZ
## Network Meta-analysis vs. Placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chlorthalidone</th>
<th>Other Low-dose Diuretic</th>
<th>Indirect Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.74 (0.58-0.95)</td>
<td>0.72 (0.54-0.95)</td>
<td>1.03 (0.71-1.48)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.63 (0.51-0.80)</td>
<td>0.71 (0.60-0.85)</td>
<td>0.90 (0.70-1.17)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.53 (0.39-0.73)</td>
<td>Not reported</td>
<td>Not available</td>
</tr>
<tr>
<td>CVD events</td>
<td>0.70 (0.61-0.80)</td>
<td>0.76 (0.66-0.87)</td>
<td>0.92 (0.76-1.11)</td>
</tr>
<tr>
<td>CVD death</td>
<td>0.80 (0.61-1.04)</td>
<td>0.79 (0.65-0.94)</td>
<td>1.01 (0.74-1.39)</td>
</tr>
<tr>
<td>Death</td>
<td>0.89 (0.75-1.06)</td>
<td>0.91 (0.79-1.03)</td>
<td>0.98 (0.79-1.21)</td>
</tr>
</tbody>
</table>

SHEP, SHEP-pilot  EWPHE, MRC-E, PATS

*JAMA. 2004;292;43-44*
## Outcomes in Diuretic Trials

<table>
<thead>
<tr>
<th>Chlorthalidone</th>
<th>Hydrochlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDFP (beat RC)</td>
<td>VACSGAA (beat placebo, with help)</td>
</tr>
<tr>
<td>MRFIT (beat HCTZ)</td>
<td>MRFIT (lost to chlorthalidone)</td>
</tr>
<tr>
<td>SHEP (beat placebo)</td>
<td>HAPPHY (tied β-blockers)</td>
</tr>
<tr>
<td>TOMHS (no data)</td>
<td>MAPPHY (lost to metoprolol)</td>
</tr>
<tr>
<td>VHAS (tied CCB)</td>
<td>MRC-E (beat placebo, atenolol)</td>
</tr>
<tr>
<td>ALLHAT (beat all 3 competitors)</td>
<td>MIDAS (tied CCB)</td>
</tr>
</tbody>
</table>

6-0-1                                    4-3-4

6-0-1                                    4-3-4
Initial Antihypertensive Drugs for Heart Failure Prevention: Network and Bayesian Meta-analyses of Clinical Trial Data

William J. Elliott, M.D., Ph.D., Sanjib Basu, Ph.D. and Peter M. Meyer, Ph.D.

RUSH Medical College of RUSH University at RUSH University Medical Center, Chicago, IL

Lowering BP and Incident HF

- Meta-analyses of clinical trial data suggest that antihypertensive drug therapy prevents about 50% of heart failure (vs. placebo).
- The BPLTTC reported no significant relationship between blood pressure-lowering and incident heart failure.
- **Question:** Is an initial drug from one antihypertensive drug class better than others in preventing heart failure in clinical trials in hypertension?

# Meta-Analytical Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Fixed Effects”</td>
<td>One vs. all other</td>
<td>Inhomogeneity; Multiple comparisons</td>
</tr>
<tr>
<td>“Random Effects”</td>
<td>One vs. all other</td>
<td>Wider CI*s; Multiple comparisons</td>
</tr>
<tr>
<td>Network</td>
<td>Many classes; Direct &amp; indirect comparisons</td>
<td>Incoherence; Multi-arm trials</td>
</tr>
<tr>
<td>Bayesian</td>
<td>Many classes; Multi-arm trials OK; No prior hypotheses</td>
<td>Wider “CrI†”s; No measure of internal consistency</td>
</tr>
</tbody>
</table>

*CI = 95% confidence interval; †"CrI" = 2.5-97.5% credible interval
Network Meta-analysis Results

Placebo
1.87 (1.57-2.22), \( P < 10^{-11} \)

CCB
1.45 (1.28-1.65), \( P < 6 \times 10^{-9} \)

\( \beta \)-Blocker
1.32 (1.13-1.53), \( P < 3 \times 10^{-4} \)

ARB
1.25 (1.05-1.50), \( P < 0.008 \)

ACE-I
1.19 (1.05-1.36), \( P < 0.02 \)

Diuretic (referent)

Odds Ratio (95% Conf. Int.)

Worse than diuretic

Odds Ratio

\( \omega = 0.000006 \)
Bayesian Meta-analysis Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Posterior Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.00 (1.68-2.44)</td>
</tr>
<tr>
<td>CCB</td>
<td>1.87 (1.57-2.22)</td>
</tr>
<tr>
<td>(\beta)-Blocker</td>
<td>1.45 (1.26-1.68)</td>
</tr>
<tr>
<td>ARB</td>
<td>1.45 (1.28-1.65)</td>
</tr>
<tr>
<td>ACE-I</td>
<td>1.32 (1.11-1.56)</td>
</tr>
<tr>
<td>Diuretic (referent)</td>
<td>1.32 (1.13-1.53)</td>
</tr>
</tbody>
</table>

Posterior Probability (2.5-97.5% Cred. Int.)

99,000 iterations
Sensitivity Analyses

• These results were quite robust to many changes in initial conditions; for example,

• Inclusion of
  – Placebo-controlled "add-on" trials (e.g., ACTION, PART-2, PREVENT, etc.)
  – Trials in which not all patients had hypertension (e.g., HOPE, EUROPA, PEACE, Jikei Heart)
  – The hypertensive subgroup in ACTION
  – "Switching" of initial therapies (β-Blocker to Diuretic) in STOP-1, CAPPP, STOP-2, NORDIL

• Omission of ALLHAT (!)
Chlorthalidone vs. HCTZ (vs. Other)

Placebo

CCB

β-Blocker

ARB

ACE-I

HCTZ

Chlorthalidone

Worse than Chlorthalidone

Worse than HCTZ

Odds Ratio

Placebo

CCB

β-Blocker

ARB

ACE-I

HCTZ

Chlorthalidone

1.32

2

2.5

1

1.32

1.67

2

2.5

93% of Incident HF

5%
Our Conclusions

• As in the 2003 network meta-analysis by Psaty et al., that included only 30 of these trials (and 114,761 subjects), any active antihypertensive drug prevented heart failure significantly better than placebo (all $P < 0.003$).

• Overall, in both network and Bayesian meta-analyses, an initial diuretic prevented heart failure better than any other initial antihypertensive drug (all $P < 0.02$).

\(^4\textit{JAMA.} 2003;\textbf{289}:2534\)
Which BP Drugs Prevent HF Best?

- Randomized controlled clinical trials involving hypertensive or “high-risk” patients from 1997-2009 were meta-analyzed using Bayesian techniques.
- Drug classes included: $\alpha$-blocker (AB), ACE-inhibitors (ACEIs), ARBs, $\beta$-blockers (BBs), calcium channel blockers (CCBs), “conventional therapy” (CT), diuretics (DD) and placebo.
- The authors concluded that an initial diuretic prevents heart failure better than any other drug class.

Arch Intern Med. 2011;171:384-94
BP Drugs Prevent Heart Failure?

Prevention of HF by BP Drugs

Odds Ratio (95% CI), p < 0.000008

Chlorthalidone 0.59 (0.50-0.69), 3E-10
Other diuretic 0.61 (0.49-0.76), 2E-05
ACE-inhibitor 0.71 (0.63-0.80), 2E-08
CT 0.72 (0.59-0.86), 0.0004
ARB 0.81 (0.72-0.91), 0.0004
CCB 0.83 (0.74-0.94), 0.003
Beta-blocker 0.84 (0.70-1.01), 0.07
Placebo referent

Alpha-blocker 1.09 (0.82-1.44), 0.54

Arch Intern Med. 2011;171:472-3
NICE 2011 Hypertension Guidelines

• After a systematic review of all studies involving HCTZ, CTD, indapamide, and bendroflumethiazide, NICE recommended:

• “If a diuretic is required, choose a thiazide-like diuretic, such as chlortalidone (12.5-25 mg once daily) or indapamide (2.5 once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.”

Conclusions

• Chlorthalidone and HCTZ are both diuretics, but they differ with regard to:
  – PK/PD, with CTD having a much longer duration of action
  – BP lowering efficacy (CTD more potent)
  – Metabolic effects (K⁺, glucose, cholesterol, urate?)
  – Outcomes in MRFIT (CTD was superior in 1970s)
  – Precision of estimate in heart failure prevention
  – Prevention of other CVD endpoints?

• We have therefore proposed adding “HCTZ” to the “DO NOT USE” abbreviations list!